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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,656	BROWN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-22* is/are pending in the application.

4a) Of the above claim(s) *7, 9-11, 13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,12 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/GB04/00116 filed 01/13/2004 and claims priority to SWEDEN 03001039 filed 01/16/2003.

Claims 1-5, 7-22 are pending.

Claim Rejections/Objections Withdrawn

2. The rejections of claims 2-4, 12, 19-20 under 112 1st paragraph for scope of enablement is withdrawn based upon the claim amendments, and while certain R1's are prophetic the fact that it should be relatively easily to prepare ***some*** undisclosed analogs via reductive amination of the piperidines with an appropriate aldehyde and test them for activity. The rejection of claim 1 under 112 2nd paragraph for the misuse of the term "C_{2-6}heteroaryl" is withdrawn. The term "C_{2-6}heteroaryl" is broad but not indefinite, thus the 112 2nd rejection is withdrawn.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

3. The rejection of claim 1 under 112 2nd paragraph for the misuse of the term "C_{6-10}-aryl" and is maintained. The applicant's representative has not addressed the fact that "C_{6-10}-aryl" includes compounds that cannot be aromatic and thus do not actually exist for example compounds with 7, 8 and 9 carbon atoms and are in fact indefinite. Instead the applicants' representative has urged the examiner to withdraw the rejection since one of ordinary skill would realize that this only includes phenyl and naphthyl. Since naphthyl is not listed explicitly nor exemplified the examiner would like to "suggest claim language to applicants to improve the

clarity or precision of the language used". Since phenyl was apparently intended, it is suggested that phenyl be used to replace "C_{6-10}-aryl".

The rejection of claims 1-5, 8, 12, 19-22 under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905, is maintained. The applicants' representative has argued that the examiner has not characterized the prior art properly by the remarks at pg. 13,

"As a preliminary matter, Applicants point out that the '792 patent does not set forth the generic structure depicted at page 7 of the Office Action. Rather, the '792 patent teaches a broad genus and a few species encompassed within the genus wherein the NRC(=O)OR group substituted in the para position."

Contra to this assertion, the '792 document teaches twenty six compounds 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 92, 94, 95, 96, 98, 99, 102, 103, 107, 110, 111, 112, 114, 115, 118, & 119, which bear the carbamate moiety. It is unclear what the applicant's representative definition of "few" encompasses, but 26 is more than a few.

The applicants' representative has further traversed the rejection by stating that the references – "fails to identify a single compound with or without the exact core of the presently claimed invention containing a phenyl group with a para-substituted -C(=O)NR'R" group AND a meta-substituted -N(R')C(=O)OR". The examiner agrees and submits that if that were the case a 102 rejection would have been made, however in the instant case it is the teaching of the '792 patent in view of the Wei teaching. While applicants' representative assert that the Wei teaching "Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead **to some highly potent *δ* agonists**." is "no more than an invitation to go fishing", the so

called "fishing" would clearly start with those substituents previously exemplified and associated with activity such as the carbamate exemplified in the previous 26 compounds in the '792 document.

The rejection of claims 1 & 8 under 112 1st paragraph is maintained, The applicants' representative has taken issue with the examiner's citation of references showing the unpredictability in the development of opioid receptor ligands, by pointing out that no references specifically disclose the exact compounds of the specification. It is noted that these references all describe opioid receptor ligands, including small molecule ligands which, at least in the case of the Carson et. al. references, are remarkably similar to those of the instant claims. Unless the compounds of the instant case possess a pharmacophore that is impervious to activity changes effected by chemical modification, it is reasonable to believe that new compounds of similar structure will be limited in a similar manner. It is noted that the specification has limited data for the vast number of compounds claimed and does not support the contention that structural modification does not affect the activity. At least for the substituent R1, only very minor variations were made yet the claims are not commensurate in scope. It is unclear how one arrives at the generic description "C_{2-6}heteroaryl" based on the disclosure.

See *Ex parte WEIL AND SCHLICHTING*, 158 USPQ 620 (Bd. Pat. App. & Int. 1967)

"We will sustain this rejection of the claims as we are in accord with the examiner's position. We find no support in the disclosure for such compounds encompassed by these claims wherein R 1, R 2, R 3, and R 5are all the same and selected from the group, lower alkyl , hydroxy , alkoxy , di(loweralkyl)amino and nitro for example. These claims appear to be in the nature of a paper concept wherein all possible substituents have been included in the composition. There are no examples of such compounds which are included within the vast scope encompassed by these claims, although appellants have a considerable disclosure with respect to certain components but this does not warrant claims of the enormous breadth recited."

See Ex parte Herzog, Hershberg, and Coan, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating:

"it becomes obvious that the expressions defining the organic acids used.....are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification."

In addition see *In re Fouche* 169 USPQ 429 which dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

and *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976):

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing

the desired result." See In re Ellis, 37 App. D. C. 203; In re Dosselman, 37 App. D. C. 211; In re Langmuir, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (affirmed):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the invention claimed shall be no broader than the invention set forth in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only certain aryl radicals and certain specifically substituted aryl radicals would be suitable for such purposes."

The examiner has rejected the amended claim 1 under 112 1st paragraph for new matter. The amendment to claim 1 is extensive and support cannot be found in the specification. The statements in the response do not clarify this matter. As per MPEP 2163.06 "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure." The specification is 45 pages in length and no particular line is pointed to for each amendment, rather the applicants' representative states that "support for which can be found throughout the specification." The examiner has not found support for the variable definition "-O-C1-6alkyl" and certainly not in the particular context of the R1-R5 groups.

The double patenting rejections are maintained for the reasons of record.

Claim Rejections - 35 USC § 112 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "C_6-C_{10} aryl". From the specification we know that the terms "aryl" and are meant to describe aromatic compounds.

> The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (e.g., 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

Presumably "C_6-C_{10} aryl" is meant to include compounds having 7, 8, & 9 carbon atoms, such compounds cannot be aromatic. For a discussion of aromaticity see Jones, M. *Organic Chemistry* Norton: New York, 1997, pgs. 578-591. The examiner believes this is meant to be phenyl and naphthyl for C_6-C_{10} aryl. A clarification and appropriate correction is required.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-5, 8, 12, 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905 cited on the IDS. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

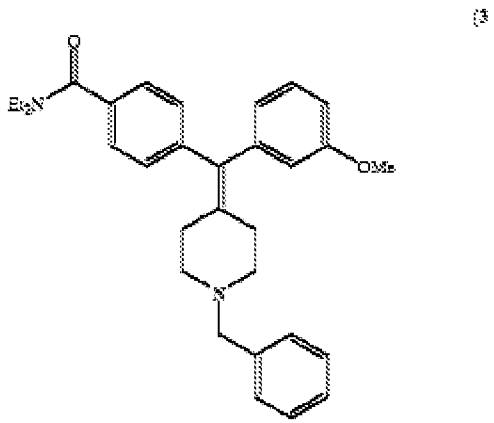
Determination of the scope and content of the prior art

(MPEP 2141.01)

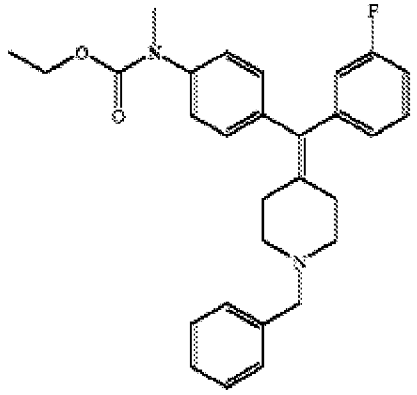
The U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 documents all teach a large group of compounds bearing essentially the same piperidinyl-diphenylmethane core. These compounds have the same utility, namely as δ-opioid agonists, selective over the other opioid receptor subtypes. A few examples are shown below:

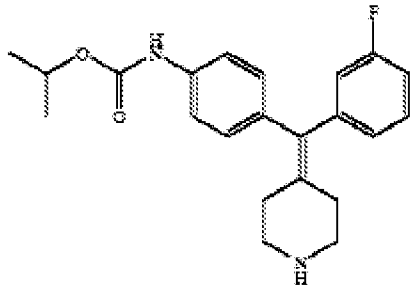
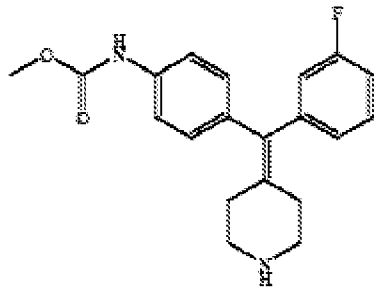
EXAMPLE 23

Preparation of N,N-Diethyl-4-[(N-benzyl)-3-methoxyphenyl-piperidin-4-ylidene-methyl]-benzamide (compound 37)



Most compelling are the compounds bearing the carbamate group as shown in Table 1.

Example	Compound	Chemical structure
61	108	

Example	Compound	Chemical structure
67	99	
68	98	

Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel.....and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905 teaches that while the phenyl ring bearing the dialkylamide group was important for activity, other features in particular the

substituents on the other phenyl ring (i.e. the methoxy group of SNC-80) were less sensitive to changes and that preparing compounds with such modifications would likely be the right place to look for more potent compounds. In the author's own words:

"Initial SAR studies1[5] around SNC-80 indicated that the 4-N,N-diethylaminocarbonyl group is a key structural feature, but neither the methoxy group, the allyl group, nor the two methyl groups on the piperazine were essential for high affinity at the δ opioid receptor." (pg. 2895 column 2)

"The opioid receptor binding affinity, selectivity, and agonist potency of the target compounds **6** are listed in Table 1, and those of SNC-80, diarylmethylpiperazine **4**, and diarylmethylpiperidine **5** are also included for comparison. As compared to SNC-80 [δ– IC_{50}) 1.31 nM; μ/δ =245; κ/δ = 1890 (*K*i) 4 nM; μ/δ=990 on rat brain membranes)[18]], compound **6f** displayed similar binding affinity [IC_{50}) 1.56 nM (*K*i) 5 nM; μ/δ > 1200 on rat brain membranes)18] on δ receptors but an improved selectivity over μ and κ receptors (μ/δ = 3370; κ/δ > 6410). **6a**, a derivative of **6f** without the 3-MeO group on the phenyl ring, even further increased selectivity as a result of improved δ -affinity (IC50) 0.87 nM; μ/δ= 4370; κ/δ = 8590). **Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead to some highly potent δ agonists**." (pg. 3897 column 2, Results and Discussion)

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs only in the substitution of the carbamate group on one of the phenyl rings, at least where R_1 is phenyl of the instant case. This relationship is shown graphically in Figure 1.

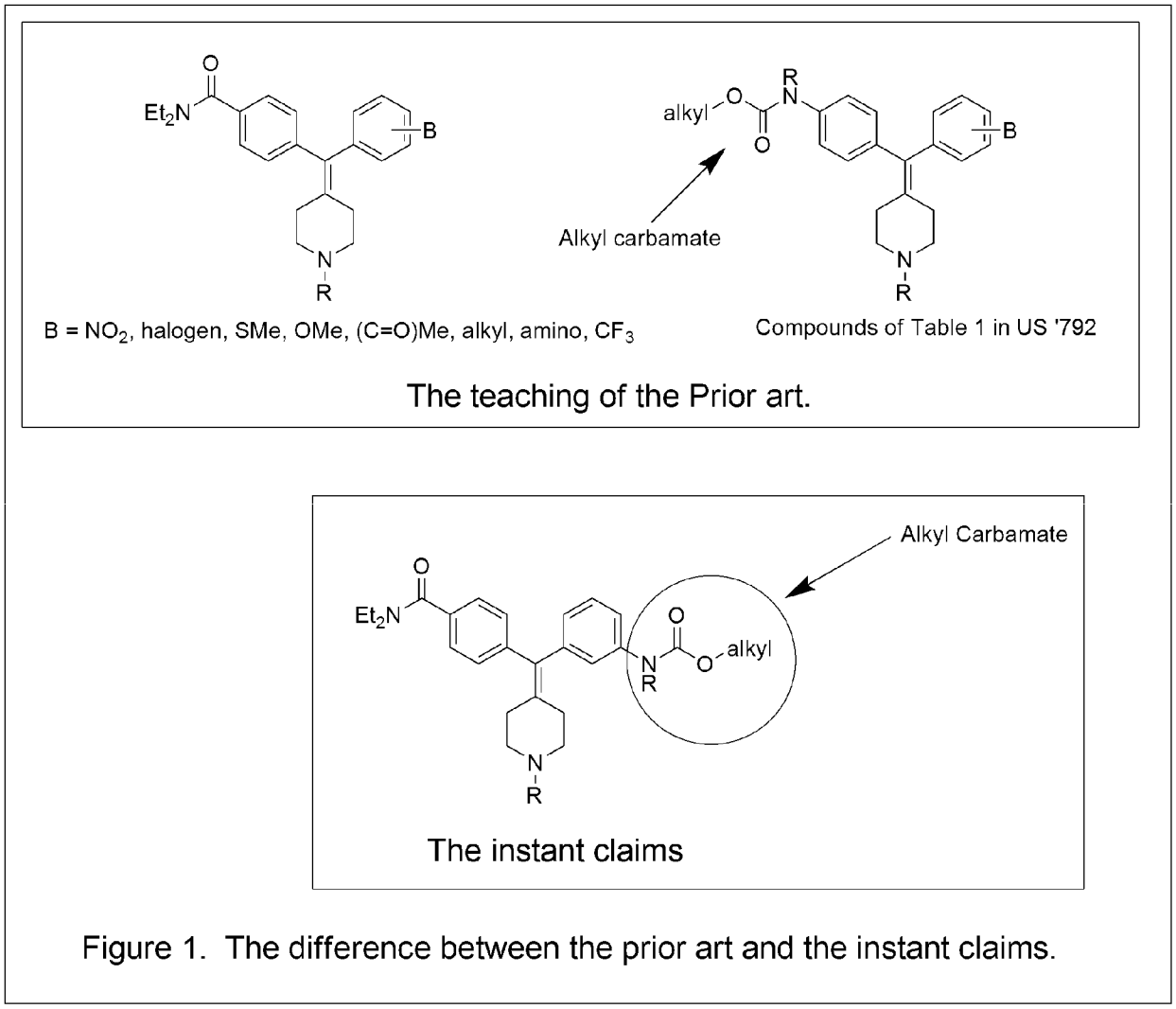


Figure 1. The difference between the prior art and the instant claims.

(MPEP 2141.02)

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of U.S. 6,187,792 OR U.S. 6,455,545, OR WO9828275 to produce the instant invention. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds by the suggestion

of Wei et. al. who stated that "Considerable variation is possible in the nature of the substitution on the phenyl ring, and this can lead to some highly potent δ agonists." The variation of the instant case was a known modification as shown by the compound of Table 1 in the '792 patent.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1 & 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendments to the definition of R1-R5 as "-O-C1-6alkyl" describes a new genus that does not find support in the specification as filed. This is a new matter rejection.

8. Claims 1 & 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds corresponding to Formula (I), it does not reasonably provide enablement for the long list of potential groups R_1, in particular the prophetic heterocycles of "C_{2-6}heteroaryl" . The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a medicinal chemistry invention requiring the synthesis of compounds and these compounds must have the utility of treating pain or at least as ligands at opioid receptors. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing medicinal chemist. The following Wand factors will be discussed in detail below: **(C) The state of the prior art: (E) The level of**

predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:

While little information was given in the specification, the examiner would like to point the applicant's attention to the tables 1 & 2, which reveal the level of activity at the δ, κ, and μ opioid receptors for only four compounds. (**F**) & (**G**)

Table 1

Compound #	Human δ (nM)			Human κ (nM)	Human μ (nM)	RAT BRAIN (nM)	
	IC_{50}	EC_{50} (high)	%EMax (high)	IC_{50}	IC_{50}	EC_{50}	%EMax
3	0.48	0.62	91.7	188	28.7	N/A	N/A

Table 2

Compound #	Human δ (nM)			Human κ (nM)	Human μ (nM)
	IC_{50}	EC_{50} (low)	%EMax (low)	IC_{50}	IC_{50}
1-2, 5	0.30-0.35	1.80-5.97	93.7-127.8	235.5-865.3	62.8-498

In order to further clarify as to what activity at these opioid receptors is and to make the record extremely clear that that examiner is not taking official notice of this fact, but rather that this conclusion is based on the objective statements of those in the art, the following discussion and publications are submitted that describe exactly what is meant by “activity” or “inactivity”.

It is an art recognized phenomenon in pharmacology that compounds having activity above a certain threshold are inactive, meaning that they do not have that activity. In binding assays (like those of the instant specification) the general threshold is 10 uM or 10,000 nM.

At the very same receptors of the instant case Calo et. al. *British Journal of Pharmacology* **2002**, 136, 303 - 311.

> "UFP-101 **was essentially inactive at DOP and MOP sites, where about 30% inhibition of [3H]-diprenorphine binding was observed at 10 μM UFP-101**."

And Chang et. al. MOLECULAR PHARMACOLOGY, **1984**, *26*, 484-488, describing opioid ligands:

> "When guinea pig brain membrane in the presence of ιz- and #{244}-ligands is used as K-sites source and [3H] diprenorphine as labeled ligand, EKC is a potent competitor but DADLE is **virtually inactive and the IC50 value is about 10 μM** (Fig. 3). Again, these data are consistent with the data reported by Corbett et al. (24) that **DADLE is virtually inactive as a K-ligand.**"

And Kruzsynski et. al. *Journal of Peptide Research* **2005**, 66, 125-131: "These two compounds were weak l-antagonists in the GPI assay and **were inactive in the MVD assay** (Tables 2 and 3)." [referring to compounds 4 and 5]

Table 3. **GPI and MVD assay of endomorphin-2 analogs**

		GPI		MVD	
Peptide number	Sequence	IC_{50} (nM)[a]	K_e (nM)[a,b]	IC_{50} (nM)[a]	MVD/GPI IC_{50} ratio
1	Tyr-Pro-Phe-Phe-NH_2 (endomorphin-2)	7.71 ± 1.47		15.3 ± 1.8	1.98
2	Tyr-Pro-Phe-1-Nal-NH_2	1130 ± 240		>10 000	
3	Tyr-Pro-Phe-2-Nal-NH_2	150 ± 11		1340 ± 80 (IC_{50})[c]	8.93
4	Tyr-Pro-Phe-D-1-Nal-NH_2		1250 ± 40	>10 000	
5	Tyr-Pro-Phe-D-2-Nal-NH_2		1260 ± 50	Inactive	

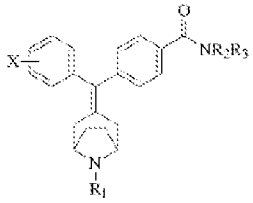
a. Mean of three to five determinations (± SEM).
b. Determined against TAPP (Tyr-D-Ala-Phe-Phe-NH_2).
c. Partial agonist (maximal inhibition of electrically induced contractions = 70%).

In a closely related series of compounds, a more modest definition of activity was given, John R. Carson et. al. "N-Alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)phenylmethyl]-benzamides, μ and δ opioid agonists" *Bioorganic & Medicinal Chemistry Letters* **2004**, *14*, 2113-2116

"The opioid binding affinities of analogues of 3 are shown in Table 1. Interestingly, compound 3 itself was found to embody the optimal structural features within this new structural subclass of l agonists. A secondary amide is necessary for significant l agonist activity. The group attached to the nitrogen of the secondary amide could not deviate far in size from ethyl in order to retain good μ activity. **Methyl, n-propyl, cyclopropyl, and 2-fluoroethyl retained activity but 2-methoxyethyl, N-cyclohexyl, and N-phenyl were inactive.**"

The relevant portion of Table 1 of Carson et. al. is shown below:

Table 1. Opioid receptor binding



Compd	R_1	R_2,R_3	X	Stereochemistry	δ K_i, nM	μ K_i, nM	μ/δ
2	2-Phenethyl	Et_2	H	1*R*,5*S*	0.24	72	305
3	2-Phenethyl	H,Et	H	1*R*,5*S*	46.7	0.26	0.0056
7	2-Phenethyl	Et_2	H	1*S*,5*R*	42.1	317	7.53
8	2-Phenethyl	H,Et	H	1*S*,5*R*	4.69	7.16	1.53
9	2-Phenethyl	H,*n*-Pr	H	*rac*	22	1.6	0.073
10	2-Phenethyl	H_2	H	*rac*	35.9	39.6	1.1
11	2-Phenethyl	H,*n*-Bu	H	*rac*	49.3	21.7	0.44
12	2-Phenethyl	H,Me	H	*rac*	13	0.14	0.011
13	2-Phenethyl	H,cycloPr	H	*rac*	20	1.01	0.05
14	2-Phenethyl	H,cyclohexyl	H	*rac*	924	717	0.78
15	2-Phenethyl	H,2-methoxy-ethyl	H	*rac*	103	163	1.58
16	2-Phenethyl	H,2-thiazolyl	H	*rac*	49.53	53	1.08
17	2-Phenethyl	H,2-fluoroethyl	H	*rac*	32	2.99	0.093
18	2-Phenethyl	H,*t*-Bu	H	*rac*	352	608	1.73
19	2-Phenethyl	H,phenyl	H	*rac*	1517	4242	2.8

It is clear that Carson regards compounds **14**, **15**, and **19** as inactive, and compound **15** has an activity of 103 nM. According to Carson compounds with activity of greater than 100nM are inactive. The rather stringent definition of Carson may be debatable, however when comparing the R2 and R3 definitions of the instant case to those of Carson, it is clear that this position

profoundly affects the activity. The instant claims exemplify only alkyl and yet are drawn toward a laundry list of "optionally substituted groups".

Morevover in relation to the R1 definition "C_{2-6}-heteroaryl" of the instant case to the heteroaryls disclosed by Carson the unpredictable nature of these changes are clear. While Carson show a modest group of "heteroaryls"(indole, pyrrole, thiophene, imidazole, and pyridine), as in Table 1, changes to this group results in large changes in activity. Compare compounds 22 (indole) and compound 27 (pyrrole) to the thiophene derivative 44.

22	2-(3-Indolyl)-ethyl	R,Et	H	rac	23.7	84	3.55
23	5-Methyl-imidazol-4-methyl	R,Et	H	rac	35.9	81	3.88
24	3-Hydroxyethyl	R,Et	H	rac	26.17	76	2.89
25	Imidazol-4-ylmethyl	R,Et	H	rac	3.88	103	25.9
26	2-Pyridylmethyl	R,Et	H	rac	0.86	17	59.7
27	1-Methylpyrrol-2-yl	R,Et	H	rac	28.77	59	2.83
28	H	R,Et	4-OH	rac	4.5	365	58.32
29	3,3-Dimethylallyl	R,Et	3-CH_2O	rac	0.72	2.04	2.85
30	Allyl	R,Et	3-CH_2O	rac	1.45	13.8	9.54
31	H	R,Et	3-CH_2O	rac	13.16	96.0	7.3
32	3,3-Dimethylallyl	R,Et	3-OH	rac	2.02	2.52	1.25
33	Allyl	R,Et	3-OH	rac	0.384	9.58	24.94
34	2-Phenethyl	R,Et	4-CH_2O	rac	13.29	6.1	0.54
35	3-Thienylmethyl	R,Et	4-CH_2O	rac	1.32	13.48	10.23
36	2-Chlorobenzyl	R,Et	4-CH_2O	rac	5.67	122	21.63
37	2-Phenethyl	R,Et	4-OH	rac	7.8	21.7	2.79
38	2-Thienylmethyl	R,Et	4-OH	rac	0.25	6.77	27.05
39	2-Chlorobenzyl	R,Et	4-OH	rac	0.93	8.72	9.37
40	3-Phenethyl	R,Et	3-CH_2O	rac	19.79	0.654	0.033
41	2-Thienylmethyl	R,Et	3-CH_2O	rac	0.53	3.79	7.2
42	2-Chlorobenzyl	R,Et	3-CH_2O	rac	0.66	57.74	8.67
43	2-Phenethyl	R,Et	3-OH	rac	8.18	0.222	0.05
44	2-Thienylmethyl	R,Et	3-OH	rac	0.152	0.664	4.37
45	2-Chlorobenzyl	R,Et	3-OH	rac	2.09	14.98	7.17
46	CH_3	R,Et	H	*1S,5R*	6.39	42.46	6.65
47	H	R,Et	H	*1S,5R*	5.48	74.73	13.63
48	Allyl	R,Et	H	*1S,5R*	2.24	10.52	4.69
49	CH_3	R,Et	H	*1R,5S*	292	364	1.04
50	Allyl	R,Et	H	*1R,5S*	7.75	19.09	2.47

In terms of the "heteroaryl" substituent of R^1, another teaching relevant to the instant case include Carson et. al. U.S. PG Pub 2005/009860 A1, who have reported six examples of heteroaryls, namely furan, benzothiophene, isoxazole, quinoline, thiophene, and pyridine, attached to a core similar to the instant case that are also opioid receptor ligands. The relevant data is show below for convenience:

Formula (I)

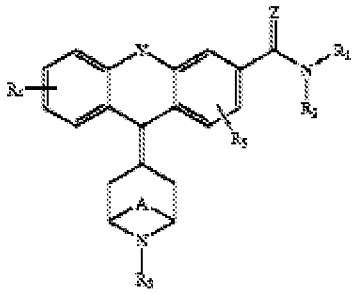


Table 1

Cpd	R_1	R_2	R_3	R_4	R_5	A	Y	Z
85	Et	Et	H	7-pyridin-4-yl	H	CH_2CH_2	O	O
86	Et	Et	H	7-furan-3-yl	H	CH_2CH_2	O	O
87	Et	Et	H	7-benzo thiophen-2-yl	H	CH_2CH_2	O	O
89	Et	Et	H	7-pyridin-3-yl	H	CH_2CH_2	O	O
90	Et	Et	H	7-thiophen 3-yl	H	CH_2CH_2	O	O
91	Et	Et	H	7-(3,5-dimethyl) isoxazol-4-yl	H	CH_2CH_2	O	O
93	Et	Et	H	7-pyrrol-2-yl	H	CH_2CH_2	O	O

96	Et	Et	H	5-pyridin-4-yl	H	CH_2CH_2	O	O
97	Et	Et	H	5-furan-3-yl	H	CH_2CH_2	O	O
98	Et	Et	H	5-quinolin-3-yl	H	CH_2CH_2	O	O
99	Et	Et	H	5-thiophen-3-yl	H	CH_2CH_2	O	O
101	Et	Et	H	5-pyridin-3-yl	H	CH_2CH_2	O	O

Biological and Mass Spectral Data

Table 2

Cmpd No.	rDOR Ki (nM)	rMOR Ki (nM)	hDOR GTPγS EC_{50}(nM)	hMOR GTPγS %I @10μM	DOR GTPγS EC_{50} (nM)	MAIT %I @ 150μmol	Parent Peak obs	MS calcd
85	3004.5	10700					466.1	465.60
86	1755	12525					455.1	454.57
87	12060	29025					421.1	520.70
89	1953	18670					466.2	465.60
90	838.15	12360					471.1	470.64
91	1351.5	6702					484.1	483.61
93	>10000	>10000					454.4	453.59
96	1.692	4224			35.3		466.1	465.60
97	1.7785	1806			13.3		455.1	454.57
98	24.54	7355					516.2	515.66
99	18.335	3488			12.5		471.0	470.64
101	9.14235	532.3			19.3		466	465.60

Compound 87 (R_4 is benzothiophene) & 93 (R_4 is a pyrrole) are inactive (or at least they don't bind to either receptor tested). The data of Carson et. al. show that identity of the heteroaryl is

important, and upon changing say from a pyridine in compound 96 to a pyrrazole in compound 93 all activity is lost. This is not really surprising, as it is well known that molecular structure is correlated with physical properties and in particular in heterocyclic chemistry the change from one ring to another often results in dramatic changes in properties. Pozharskii et. al. *Heterocycles in Life and Society* Wiley, 1997, pgs. 1-6):

> "It is rumored that the Russian scientist Beketov once compared heterocyclic molecules to jewelry rings studded with precious stones. Several carbon atoms thus make up the setting of the molecular ring, while the role of the jewel is played by an atom of another element, a heteroatom. In general, it is the heteroatom which imparts to a heterocycle its distinctive and sometimes striking properties. ..... the heteroaromatic compounds, as the most important group of heterocycles, possess, highly specific features....."

Given the diverse behavior and complete lack of activity for certain groups, such prophetic recitations as those of the instant claims should be evaluated carefully. In terms of the "heteroaryl" substituent of R_1 of the instant case the specification gives only four examples of actual compounds, in terms of the heteroaryl which are furan, thiophene, and thiazole. Based on upon the sheer unpredictability of the area of opioid receptor ligands as evidenced by the prior art, and the paucity of working examples it is readily apparent that one could not make/use this very broad invention without undue experimentation. Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-5, 8, 12, 19-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 8 of U.S. 6,187,792 in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905. See the 103 (a) rejection supra.

10. Claims 1-5, 8, 12, 19-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 of U.S. 6,455,545, in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905. See the 103 (a) rejection supra.

11. Claims 1-5, 8, 12, 19-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 13, 19, 22 of U.S. 6,693,117, in view of Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905. See the 103 (a) rejection supra.

12. Claims 1-5, 8, 12, 19-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8, 15-18 of copending Application No. 10/596,850, in view of U.S. 6,187,792 and Wei, Z. et al., "N,N-Diethyl-4-(phenylpiperidin-4-ylidenemethyl)benzamide: A Novel...and its Analogues," *Journal of Medicinal Chemistry*, **2000**, *43*, 3895-3905. The claims of the instant case differ from those of the '850 application in the identity of R1. At least where R1 is phenyl of the instant case, the alkyl, cycloalkyl, and H derivatives of the '850 application are equivalents as taught by the secondary references.

This is a provisional obviousness-type double patenting rejection.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625
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